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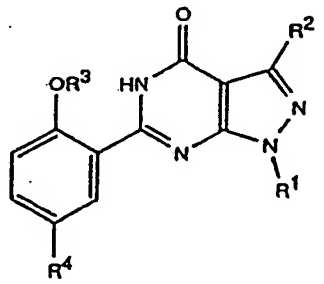
(54) Title: PYRAZOLOPYRIMIDINONE ANTIANGINAL AGENTS



(I)

(57) Abstract

Compounds of formula (I), and pharmaceutically acceptable salts thereof wherein $R^1$ is $C_1$-$C_6$ alkyl; $R^2$ is H, methyl or ethyl; $R^3$ is $C_2$-$C_4$ alkyl; $R^4$ is $C_1$-$C_4$ alkyl optionally substituted with $NR^5R^6$, CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkenyl optionally substituted with CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkanoyl optionally substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or halo; $R^5$ and $R^6$ are each independently H or $C_1$-$C_4$ alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, 4-($NR^8$)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted by one or two $C_1$-$C_4$ alkyl groups; $R^7$ is H or $C_1$-$C_4$ alkyl; and $R^8$ is H, $C_1$-$C_3$ alkyl or hydroxy $C_2$-$C_3$ alkyl; are selective cGMP PDE inhibitors useful in the treatment of cardiovascular disorders such as angina hypertension, heart failure and atherosclerosis.

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# PYRAZOLOPYRIMIDINONE ANTIANGINAL AGENTS

This invention relates to a series of pyrazolo[3,4-d]pyrimidin-4-ones, which are potent and selective inhibitors of cyclic guanosine 3′,5′-monophosphate phosphodiesterase (cGMP PDE), having utility in a variety of therapeutic areas including the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

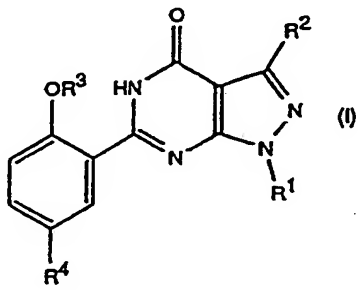
The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3′,5′-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

European patent application EP-A-0349239 discloses a group of 1-unsubstituted pyrazolo[3,4-d]pyrimidin-4-ones as cGMP PDE inhibitors with bronchodilator and vasodilator activity of value in combatting asthma, bronchitis, angina, hypertension and congestive heart failure.

European patent application EP-A-0201188 discloses certain pyrazolo[4,3-d]pyrimidin-7-ones as adenosine receptor antagonists and PDE inhibitors, useful in the treatment of cardiovascular disorders such as heart

failure or cardiac insufficiency. However these compounds are neither particularly potent PDE inhibitors, nor are they claimed to be selective inhibitors of cGMP PDE.

The compounds of the present invention have the formula (I):



(I)

wherein $R^1$ is $C_1$-$C_6$ alkyl;

$R^2$ is H, methyl or ethyl;

$R^3$ is $C_2$-$C_4$ alkyl;

$R^4$ is $C_1$-$C_4$ alkyl optionally substituted with $NR^5R^6$, CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkenyl optionally substituted with CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkanoyl optionally substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or halo;

$R^5$ and $R^6$ are each independently H or $C_1$-$C_4$ alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, 4-($NR^8$)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted by one or two $C_1$-$C_4$ alkyl groups;

$R^7$ is H or $C_1$-$C_4$ alkyl;

and $R^8$ is H, $C_1$-$C_3$ alkyl or hydroxy $C_2$-$C_3$ alkyl;

and pharmaceutically acceptable salts thereof.

In the above definition, unless otherwise indicated, alkyl and alkoxy groups having three or more

carbon atoms may be straight chain or branched chain. In addition, alkenyl and alkanoyl groups having four carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein $R^1$ is n-propyl; $R^2$ is H or methyl; $R^3$ is ethyl or n-propyl; $R^4$ is ethyl substituted with $CONR^5R^6$ or $CO_2R^7$; vinyl substituted with $CONR^5R^6$ or $CO_2R^7$; acetyl substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or bromo; $R^5$ and $R^6$ together with the nitrogen atom to

which they are attached form a morpholino, 4-($NR^8$)-1-piperazinyl or 2,4-dimethyl-1-imidazolyl group; $R^7$ is H or t-butyl; and $R^8$ is methyl or 2-hydroxyethyl.

Particularly preferred individual compounds of the invention include:

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

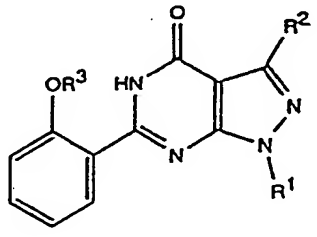
6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and 3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one.

Depending on the nature of $R^4$, the compounds of formula (I) may be prepared by a variety of methods from a compound of formula (II):



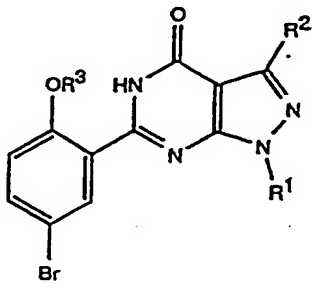

(II)

wherein $R^1$, $R^2$ and $R^3$ are as previously defined for

formula (I). For example, when $R^4$ is $C_2$-$C_4$ alkanoyl, the required product is obtainable by conventional Friedel-Crafts acylation whereby (II) is reacted with about a 2-fold excess of an acyl halide of formula ($C_1$-$C_3$ alkyl)COY, wherein Y is halo, preferably chloro or bromo, in the presence of about a 3-fold excess of a Lewis acid such as aluminium chloride or aluminium bromide, in a suitable solvent, e.g. dichloromethane, at from about 0°C to the reflux temperature of the reaction medium. When $R^4$ is $C_2$-$C_4$ alkanoyl substituted with $NR^5R^6$, wherein $R^5$ and $R^6$ are as previously defined, the product is obtained from (II) via the intermediacy of the corresponding haloketone, i.e. a compound of formula (I) wherein $R^4$ is CO($C_1$-$C_3$ alkylene)X and X is halo, preferably chloro or bromo, by reaction of the appropriate haloketone with the required amine of formula $R^5R^6NH$ in the presence of at least one equivalent of base to scavenge the liberated acid by-product (HX), in a suitable solvent, e.g. acetonitrile, at about room temperature. The base may be an inorganic salt such as anhydrous potassium carbonate, a tertiary amine such as triethylamine, or excess reactant amine. In cases wherein either $R^5$ or $R^6$ is H, it may be advantageous to use a protected amine of formula $R^5NHP$ or $R^6NHP$ wherein P is a compatible protecting group, e.g. benzyl which can be subsequently removed by catalytic hydrogenation. When both $R^5$ and $R^6$ are H, an ammonia equivalent of formula $P'_2NH$, wherein P' is a protecting group such as t-butoxycarbonyl, may be beneficially employed. In this case, the potassium salt of the non-basic aminating reagent is used for reaction with the haloketone; deprotection is effected by acidolysis using, for example, hydrogen chloride, which allows convenient isolation of the desired aminoketone as its hydrochloric salt. The intermediate haloketone is also obtained via Friedel-Crafts

chemistry, as described above, in this case between (II) and the appropriate haloacyl halide of formula $X(C_1-C_3$ alkylene)COY, wherein X and Y are as previously defined.

Compounds of formula (I) wherein $R^4$ is halo and $R^1$, $R^2$ and $R^3$ are as previously defined may be obtained from the corresponding primary amine, i.e. a compound of formula (I) wherein $R^4$ is $NH_2$, via classical sequential diazotisation-halogenation procedures including, for example, the Schiemann, Sandmeyer and Gatterman reactions. The primary amines, in turn, are obtained by nitration of (II) using, e.g. a conventional concentrated nitric acid/concentrated sulphuric acid combination, followed by reduction of the intermediate nitroarene, e.g. by catalytic hydrogenation.



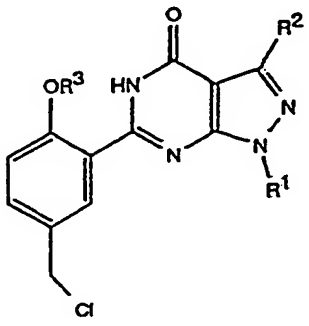

(III)

Compounds of formula (I) wherein $R^4$ is bromo, and $R^1$, $R^2$ and $R^3$ are as previously defined for formula (II), i.e. compounds of formula (III), may also be, prepared directly from compounds of formula (II) by bromination in a suitable solvent. This may be achieved, for example, either with about a 60-100% excess of N-bromosuccinimide in dimethylformamide (DMF) at room temperature or with a similar excess of bromine in glacial acetic acid at from about room temperature to about 100°C. These bromo compounds are also valuable intermediates in the synthesis of further

compounds of formula (I).

By exploitation of Heck methodology, the bromo intermediates (III) can be transformed to compounds of formula (I), wherein $R^4$ is CH=CHCN, $CH=CHCONR^5R^6$ or $CH=CHCO_2R^7$ and $R^1$, $R^2$, $R^3$, $R^5$, $R^6$ and $R^7$ are as previously defined, except that $R^7$ is not H, by employment of acrylonitrile or the appropriate acrylic acid amide or ester derivative. The reaction is generally carried out with about a 50% excess of both the alkene reagent and a tertiary amine such as triethylamine, in the presence of about 0.1 equivalents of a tertiary arylphosphine, preferably tri-o-tolylphosphine, and about 0.05 equivalents of palladium(II) acetate, in a suitable solvent such as acetonitrile, at the reflux temperature of the reaction medium. The resulting acrylic esters may be hydrolysed if desired, e.g. using aqueous sodium hydroxide solution, with methanol as co-solvent, to afford the corresponding cinnamic acids. Clearly, these cinnamic acids may be used as an alternative source of cinnamamides of formula (I) wherein $R^4$ is $CH=CHCONR^5R^6$ via the corresponding acyl halide (preferably chloride), or other activated acid derivative, by reaction with the appropriate amine of formula $HNR^5R^6$ (vide infra). Moreover, all the alkenyl products thus synthesised may be subjected to catalytic hydrogenation, e.g. using 5-10% palladium on charcoal in a suitable solvent at about 15-50 p.s.i. (1.0-3.45 bar) and room temperature, to provide compounds of formula (I) wherein $R^4$ is $CH_2CH_2CN$, $CH_2CH_2CONR^5R^6$ or $CH_2CH_2CO_2R^7$ and $R^1$, $R^2$, $R^3$, $R^5$, $R^6$ and $R^7$ are as previously defined for formula (I). An alternative reduction strategy, in which the acrylonitrile derivative (cinnamonitrile analogue) is exhaustively hydrogenated with Raney nickel in glacial acetic acid, affords compounds of formula (I) wherein $R^4$ is 3-aminopropyl and $R^1$, $R^2$ and $R^3$ are as previously defined.

The higher homologues, i.e. compounds of formula (I) wherein $R^4$ is either $C_3$-$C_4$ alkyl or $C_3$-$C_4$ alkenyl substituted with CN, $CONR^5R^6$ or $CO_2R^7$, or is 4-aminobutyl, may be derived from the alkenols obtained from Heck reactions between a bromo compound of formula (III) and either allyl alcohol or 3-buten-1-ol. The conventional procedures necessary for transformation of the terminal hydroxyl group via a suitably reactive derivative, e.g. the corresponding chloride, bromide, iodide or mesylate, to the required functional groups will be well known to persons skilled in the art, and will be equally applicable to the 2-hydroxyethyl analogue(vide infra) thereby offering an alternative to Heck methodology. Compounds of formula (I), wherein $R^4$ is $CH_2CN$, $CH_2CONR^5R^6$, $CH_2CO_2R^7$ or $CH_2CH_2NH_2$, may be obtained from the chloromethyl intermediates of formula (IV) by reaction with an alkali metal cyanide, e.g. sodium cyanide or potassium cyanide, followed by standard transformations of the resulting nitrile.




(IV)

Compounds of formula (IV), wherein $R^1$, $R^2$ and $R^3$ are as previously defined for formula (III), are obtainable by subjecting compounds of formula (II) to standard chloromethylation conditions, e.g. paraformaldehyde and concentrated hydrochloric acid, at from about room temperature to about 120°C.

As a general alternative to the above Heck reaction approach, the desired alkenes (and derived

alkanes via catalytic hydrogenation) may be obtained using a Wittig-Horner strategy in which an aldehyde of formula (I), wherein $R^4$ is CHO and $R^1$, $R^2$ and $R^3$ are as previously defined, is reacted with the appropriate phosphonium salt or phosphonate in the presence of a suitable base. The aldehyde itself is obtainable by formylation, e.g. using DMF, of the aryllithium derivative of (III) and, by analogy, is also a convenient precursor to compounds of formula (I) wherein $R^4$ is $C_2$-$C_4$ alkenyl or $C_2$-$C_4$ alkyl and $R^1$, $R^2$ and $R^3$ are as previously defined. The aryllithium derivative of (III) is readily preparable from (III) by lithium-bromine exchange, using n-butyllithium, under conventional conditions.

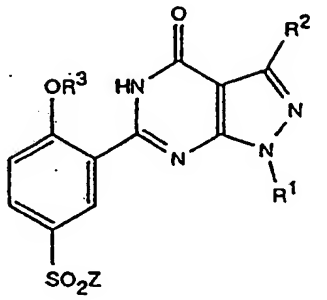
The chloromethyl intermediates of formula (IV) may also be used for the preparation of compounds of formula (I), wherein $R^4$ is $CH_2NR^5R^6$ and $R^1$, $R^2$, $R^3$, $R^5$ and $R^6$ are as previously defined, by reaction with the appropriate amine of formula $HNR^5R^6$ (or protected version thereof - vide supra). Preferably the reaction is carried out with about a 3-fold excess of amine in a suitable solvent, e.g. 2-butanone, at from about 0°C to the reflux temperature of the reaction medium. By analogy, compounds of formula (I) wherein $R^4$ is ($C_2$-$C_4$ alkylene)$NR^5R^6$ may be conveniently obtained from, e.g., the appropriate chloro, bromo, iodo or mesyloxy precursor which, in turn, are derivable from the corresponding alcohol by standard procedures.

The $C_2$-alcohol ($R^4$ is $CH_2CH_2OH$) may be obtained by reaction of the above-mentioned aryllithium intermediate with ethylene oxide, whilst the $C_3$- and $C_4$-alcohols can be prepared by catalytic hydrogenation of the alkenols obtained when a bromo compound of formula (III) is subjected to Heck reaction conditions with allyl alcohol or 3-buten-1-ol respectively (vide supra).

The chloromethyl intermediates (IV) may be further employed to furnish the corresponding methyl derivatives, i.e. compounds of formula (I) wherein $R^4$ is $CH_3$ and $R^1$, $R^2$ and $R^3$ are as previously defined. This can be achieved by catalytic hydrogenation using a palladium on charcoal catalyst, in a suitable solvent such as ethyl acetate, at about 50 p.s.i. (3.45 bar) and room temperature. By analogy, when $R^4$ is ethyl, n-propyl or n-butyl, such compounds of formula (I) may also be obtained from the corresponding alkyl chlorides derived, in turn, from the appropriate alcohols mentioned above by standard methodology. Other alcohol derivatives, e.g. the corresponding bromide, iodide or mesylate, may also be used.

The aryllithium intermediates are also useful in the preparation of compounds of formula (I) wherein $R^4$ is $CONR^5R^6$ or $CO_2R^7$ and $R^1$, $R^2$, $R^3$, $R^5$, $R^6$ and $R^7$ are as previously defined. For example, lithiation of (III) in dry tetrahydrofuran (THF) at about -78°C using about a 2 to 3-fold excess of a solution of n-butyllithium in hexane, quenching of the resulting aryllithium with carbon dioxide at from about -70 to 0°C, and aqueous acidic work-up at about room temperature, furnishes the corresponding benzoic acid derivative. The acid may be activated under mild conditions, such as those obtaining in peptide bond formation *via* amino acid coupling procedures, and converted to an ester or amide derivative as required. For example, activation of the benzoic acid using a carbodiimide/1-hydroxybenzotriazole combination in the presence of the required amine of formula $HNR^5R^6$ or alcohol of formula $R^7OH$, in a suitable solvent such as dichloromethane at about 0°C to room temperature, yields the corresponding amide or ester respectively. Alternatively, the acyl halide, most conveniently the acyl chloride, may be used as the required intermediate.

Compounds of the formula (I) wherein $R^4$ is $SO_2NR^5R^6$ and $R^1$, $R^2$, $R^3$, $R^5$ and $R^6$ are as previously defined may be prepared by the reaction of a compound of formula (V):



(V)

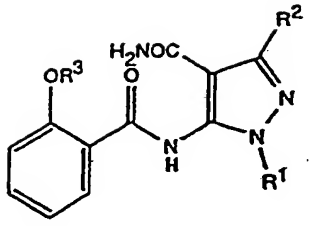
wherein $R^1$, $R^2$ and $R^3$ are as previously defined for formula (IV), and Z is fluoro, chloro or bromo, preferably chloro, with a compound of formula (VI):

$$HNR^5R^6 \qquad (VI)$$

wherein $R^5$ and $R^6$ are as previously defined. The reaction is generally carried out at room temperature, preferably in the presence of a solvent, for example a $C_1$-$C_3$ alkanol, using a 2 to 5-fold excess of (VI) to scavenge the acid by-product (HZ).

Compounds of formula (V) are obtainable from compounds of formula (II) by the application of known methods for the introduction of a $SO_2Z$ group, wherein Z is as previously defined, into a benzene ring. For example, when Z represents a chlorine atom, by the action of chlorosulphonic acid at or near 0°C.

Compounds of formula (II) may be prepared from compounds of formula (VII):

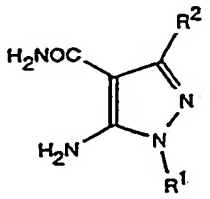


(VII)

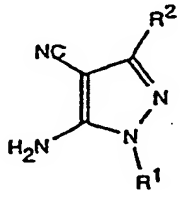
wherein $R^1$, $R^2$ and $R^3$ are as previously defined, by the application of known cyclisation methods for pyrimidinone ring formation. Thus, for example, the cyclisation may be effected by the treatment of (VII) with a base such as sodium hydroxide or potassium carbonate, optionally in the presence of hydrogen peroxide, in an ethanol-water medium at reflux temperature.

In an alternative cyclisation procedure, compounds of the formula (II) may be obtained by treatment of (VII) with polyphosphoric acid at about 140°C.

Compounds of formula (VII) may be prepared from compounds of formula (VIII):

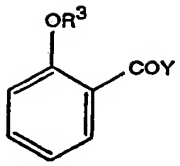


(VIII)



(IX)

wherein $R^1$ and $R^2$ are as previously defined, by reaction with compounds of formula (X):

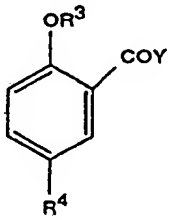



(X)

wherein $R^3$ and Y are as previously defined.

The reaction is generally carried out using about a 20% excess of (X) in the presence of an excess of a tertiary amine such as triethylamine or pyridine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylamino-pyridine, in an inert solvent such as dichloromethane at from about 0 to about 25°C for 2-24 hours. For convenience, pyridine may also be used as solvent.

Compounds of formula (I) may be obtained more directly from a compound of formula (XI):




(XI)

wherein $R^3$, $R^4$ and Y are as previously defined, when such acyl halides are readily accessible, by reaction with (VIII) and subsequent ring-closure of the product as described above. Clearly this alternative synthetic route will only be appropriate when $R^4$ is compatible with the reaction conditions obtaining in both steps.

The aminopyrazole carboxamides of formula (VIII) may be obtained by acid hydrolysis of the corresponding nitriles of formula (IX), whilst the latter, the acyl halides of formulae (X) and (XI), and the intermediates employed for introduction of the various $R^4$ substituents into compounds of formula (II) to afford compounds of formula (I), when neither commercially

available nor subsequently described, can be obtained by conventional synthetic procedures, in accordance with literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic centre may also be prepared in a conventional manner. For example a solution of the free base is treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

All of the above reactions are entirely conventional and the necessary reagents and conditions for their performance can readily be established by reference to standard textbooks and to the Examples and Preparations provided hereafter. Alternatives and variations will also be evident to persons skilled in the art to enable all the compounds defined by formula (I) to be prepared.

The biological activities of the compounds of the present invention were determined by the following test methods.

Phosphodiesterase activity

Compound affinities for cGMP and cAMP PDEs are assessed by determination of their $IC_{50}$ values (the concentration of inhibitor required for 50% inhibition of enzyme activity). The PDE enzymes are isolated from rabbit platelets and rat kidney, essentially by the method of W.J. Thompson et al. (Biochem., 1971, 10,

311). The calcium/calmodulin (Ca/CAM)-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes are obtained from rabbit platelets whilst, of the four major PDE enzymes of the rat kidney, the Ca/CAM-dependent cGMP PDE (fraction I) is isolated. Assays are performed using a modification of the "batch" method of W.J. Thompson and M.M. Appleman (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors of Ca/CAM-independent cGMP PDE.

Platelet anti-aggregatory activity

This is assessed by the determination of a compound's ability to inhibit platelet aggregation in vitro induced by platelet activating factor (PAF), and to potentiate the platelet antiaggregatory action in vitro of activators of guanylate cyclase such as nitroprusside and EDRF. Washed platelets are prepared essentially by the method of J.F. Mustard et al. (Methods in Enzymol., 1989, 169, 3) and aggregation is determined using standard turbidimetric techniques as described by G.V.R. Born, (J. Physiol. (Lond), 1962, 162, 67P).

Antihypertensive activity

This is assessed following intravenous or oral administration of a compound to spontaneously hypertensive rats. Blood pressure is recorded via a cannula implanted in the carotid artery of either conscious or anaesthetised animals.

For administration to man in the curative or prophylactic treatment of the disorders identified on page 1, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for

administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. The compounds may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus the invention provides a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing

either entity, for use in medicine.

The invention further provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS.

In a further aspect, the invention provides a method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS, in a mammal (including a human being) which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

The invention also includes any novel intermediates of formulae (II), (III), (IV) and (V) disclosed herein.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 $F_{254}$ plates. $^1$H-Nuclear magnetic resonance (NMR) spectra were recorded using either a Nicolet QE-300 or

a Bruker AC-300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

6-(2-Ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

A solution of 5-(2-ethoxybenzamido)-1-n-propyl-pyrazole-4-carboxamide (Preparation 2; 0.541 g, 0.0017 mol) and sodium hydroxide (0.10 g, 0.0026 mol) in a mixture of water (5 ml) and ethanol (1 ml) was heated under reflux for 20 hours. The cool reaction solution was extracted with dichloromethane (5 x 30 ml), then the combined extracts dried ($Na_2SO_4$) and evaporated under vacuum to give the crude product. Purification by column chromatography ($SiO_2$, 5% MeOH in $CH_2Cl_2$) afforded the title compound as a white solid (0.45 g, 89%). Crystallisation of a sample from ethyl acetate-hexane gave colourless needles, m.p. 154-155°C. Found: C,64.45; H,5.97; N,18.89. $C_{16}H_{18}N_4O_2$ requires C,64.41; H,6.08; N,18.78%.

EXAMPLE 2

6-[2-Ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

A solution of N-methylpiperazine (0.79 g, 0.0079 mol) in ethanol (10 ml) was added to a stirred suspension of 6-(5-chlorosulphonyl-2-ethoxyphenyl)-1-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Preparation 3; 0.78 g, 0.00197 mol) in ethanol (40 ml). After 2 hours at room temperature, the solvent was removed by evaporation under vacuum. The residue was partitioned between saturated aqueous sodium bicarbonate solution (20 ml) and dichloromethane (30 ml), the organic layer removed and the aqueous phase extracted with more dichloromethane (3 x 30 ml). The combined organic solutions were dried ($Na_2SO_4$) and the solvent removed by evaporation under vacuum. The residue was purified first by column chromatography ($SiO_2$, 5% MeOH in $CH_2Cl_2$) and then crystallisation from

ethyl acetate to afford the title compound as white crystals (0.35 g, 35%), m.p. 82-84°C. Found: C,51.66; H,5.72; N,16.32. $C_{21}H_{28}N_6O_4S$; 0.5 $CH_2Cl_2$ requires C,51.39; H,5.72; N,16.72%.

EXAMPLE 3

6-[2-Ethoxy-5-(morpholinoacetyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Morpholine (0.175 g, 0.002 mol) was added to a stirred suspension of 6-(5-bromoacetyl-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Preparation 4; 0.70 g, 0.0017 mol) and anhydrous potassium carbonate (0.461 g, 0.0033 mol) in acetonitrile (30 ml) and the resulting mixture stirred at room temperature for 3 hours. The solvent was removed by evaporation under vacuum, the residue partitioned between water (20 ml) and dichloromethane (30 ml), the organic phase removed and the aqueous phase extracted with dichloromethane (3 x 30 ml). The combined organic solutions were dried ($Na_2SO_4$) and the solvent removed by evaporation under vacuum to give a yellow oil. Purification by column chromatography ($SiO_2$, 5% MeOH in $CH_2Cl_2$), followed by crystallisation from ethyl acetate-hexane, provided the title compound as white crystals (0.62 g, 85%), m.p. 160-162°C. Found: C,61.96; H,6.29; N,16.32. $C_{22}H_{27}N_5O_4$ requires C,62.10; H,6.40; N,16.46%.

EXAMPLE 4

6-{2-Ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylacetyl]-phenyl}-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Prepared by the same method as Example 3 from N-(2-hydroxyethyl)piperazine (0.156 g, 0.0012 mol), 6-(5-bromoacetyl-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Preparation 4; 0.412 g, 0.001 mol) and anhydrous potassium carbonate (0.272 g,

0.002 mol) in acetonitrile (30 ml). The product was obtained as pale yellow crystals (0.34 g, 74%), m.p. 166-169°C, after crystallisation from ethyl acetate-hexane. Found: C,61.33; H,6.72; N,18.03. $C_{24}H_{32}N_6O_4$ requires C,61.52; H,6.88; N,17.94%.

EXAMPLE 5

6-[2-Ethoxy-5-(2,4-dimethyl-1-imidazolylacetyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Prepared by the same method as Example 3 from 2,4-dimethylimidazole hydrochloride (0.265 g, 0.002 mol), 6-(5-bromoacetyl-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one(0.412 g, 0.001 mol) and anhydrous potassium carbonate (0.272 g, 0.002 mol) in acetonitrile (30 ml). The product was obtained as a brown powder after crystallisation from ethyl acetate-hexane (0.10 g, 22%), m.p. 166°C (dec.). Found C,60.82; H,5.69; N,17.93. $C_{23}H_{26}N_6O_3$; 0.3 $CH_2Cl_2$ requires C,60.84; H,5.82; N,18.27%.

EXAMPLE 6

6-(5-Bromo-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

A solution of N-bromosuccinimide (1.0 g, 0.0056 mol) in DMF (10 ml) was added dropwise to a stirred solution of 6-(2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 1; 0.84 g, 0.0028 mol) in DMF (10 ml) and the resulting red solution stirred for 20 hours. The solvent was removed by evaporation under vacuum and the residue partitioned between saturated aqueous sodium bicarbonate solution (20 ml) and ethyl acetate (20 ml). The organic phase was removed and the aqueous phase extracted with ethyl acetate (3 x 30 ml). The combined organic solutions were dried and the solvent removed by evaporation under vacuum to give an orange crystalline solid.

Recrystallisation from ethyl acetate-hexane gave the title compound as colourless crystals (0.812 g, 78%), m.p. 172-173°C. Found: C,51.13; H,4.41; N,14.84. $C_{16}H_{17}BrN_4O_2$ requires C,50.94; H,4.54; N,14.85%.

EXAMPLE 7

4-Ethoxy-3-(4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo-[3,4-d]pyrimidin-6-yl)benzoic acid

n-Butyllithium (2.5 M solution in hexane, 2.0 ml, 0.005 mol) was added dropwise to a stirred solution of 6-(5-bromo-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (0.755 g, 0.002 mol) in dry THF (20 ml) at -78°C under a dry nitrogen atmosphere. The bright yellow solution was stirred for 1 hour at -78°C, then excess crushed solid carbon dioxide was added and the resulting solution was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (3 ml) was then added and the solvents removed by evaporation under vacuum. The residue was partitioned between saturated aqueous sodium carbonate solution (30 ml) and dichloromethane (30 ml), the organic phase was removed and the aqueous phase extracted with further dichloromethane (3 x 30 ml). The aqueous phase was then acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (5 x 40 ml). The combined ethyl acetate extracts were dried ($Na_2SO_4$) and the solvent removed by evaporation under vacuum to give a white solid. Crystallisation from ethyl acetate-methanol gave the title compound as a white powder (0.130 g, 19%), m.p. 277-279°C. Found: C,59.64; H,5.19; N,16.39. $C_{17}H_{18}N_4O_4$ requires C,59.64; H,5.23; N,16.37%.

EXAMPLE 8

6-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Excess oxalyl chloride (3 ml) was added dropwise to a stirred suspension of 4-ethoxy-3-(4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)benzoic acid (Exmple 7; 0.040 g, 0.0001 mol) in a mixture of DMF (1 drop) and dichloromethane (10 ml). After 2 hours at room temperature, the solvent was removed by evaporation under vacuum and the residue dissolved in dichloromethane (10 ml). Excess N-methylpiperazine (0.1 ml) was then added and the resulting mixture stirred for 15 minutes before being evaporated to dryness under vacuum. The residue was dissolved in saturated aqueous sodium bicarbonate solution (10 ml) and the solution extracted with ethyl acetate (6 x 30 ml). The combined extracts were dried ($Na_2SO_4$) and the solvent removed by evaporation under vacuum. The resulting solid was purified by column chromatography ($SiO_2$, 5% MeOH in $CH_2Cl_2$) to give the title compound as a white powder (0.028 g, 56%), m.p. 124-127°C. Found: C,62.06; H,6.26; N,19.44. $C_{22}H_{28}N_6O_3$ requires C,62.25; H,6.65; N,19.80%.

## EXAMPLE 9

### 3-Methyl-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound was prepared from 3-methyl-5-(2-n-propoxybenzamido)-1-n-propylpyrazole-4-carboxamide (Preparation 7; 5.456 g, 0.0016 mol) and sodium hydroxide (3.16 g, 0.079 mol) in a mixture of water (150 ml) and ethanol (30 ml), by the method of Example 1, and was obtained as a white solid (4.863 g, 94%) after column chromatography. A sample crystallised from ethyl acetate-hexane as colourless needles, m.p. 112-114°C. Found: C,66.35; H,6.79; N,17.12. $C_{18}H_{22}N_4O_2$ requires C,66.24; H,6.79; N,17.17%.

EXAMPLE 10

3-Methyl-6-[5-(morpholinosulphonyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound was prepared from morpholine (0.451 g, 0.0052 mol) and 6-(5-chlorosulphonyl-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Preparation 8; 0.55 g, 0.0013 mol), according to the procedure of Example 2, and was obtained as colourless needles (0.403 g, 65%), m.p. 161-163°C, after crystallisation from ethyl acetate-hexane. Found: C,55.68; H,6.16; N,14.85. $C_{22}H_{29}N_5O_5S$ requires C,55.56; H,6.15; N,14.73%.

EXAMPLE 11

6-(5-Bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound was prepared from N-bromosuccinimide (4.9 g, 0.0276 mol) and 3-methyl-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo-[3,4-d]pyrimidin-4-one (Example 9; 3.0 g, 0.0092 mol), following the procedure of Example 6, and was obtained as yellow crystals (1.11 g, 30%), m.p. 157-159°C, after crystallisation from ethyl acetate. Found: C,53.14; H,5.17; N,13.76. $C_{18}H_{21}BrN_4O_2$ requires C,53.34; H,5.22; N,13.82%.

EXAMPLE 12

(E)-3-(3-Methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxycinnamic acid t-butyl ester

To a solution of 6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 11; 2.14 g, 0.0053 mol) and triethylamine (0.81 g, 0.008 mol) in acetonitrile (4 ml), was added palladium(II) acetate (0.06 g, 0.00027 mol), tri-o-tolylphosphine (0.16 g, 0.00053 mol) and t-

butyl acrylate (1.03 g, 0.008 mol). The mixture was heated under reflux for 4 hours, cooled to room temperature and then partioned between water (30 ml) and dichloromethane (30 ml). The organic phase was removed and the aqueous phase extracted with dichloromethane (2 x 30 ml). The combined organic solutions were dried ($Na_2SO_4$) and the solvent removed by evaporation under vacuum to give a greenish brown solid. Purification by column chromatography ($SiO_2$, $CH_2Cl_2$ then 2% MeOH in $CH_2Cl_2$) and crystallisation from ethyl acetate-hexane afforded the title compound as white crystals (1.48 g, 58%), m.p. 181-182°C. Found:C,66.50; H,6.75; N,12.27. $C_{25}H_{32}N_4O_4$ requires C,66.35; H,7.12; N,12.38%.

EXAMPLE 13

(E)-3-(3-Methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxycinnamic acid

2N Aqueous sodium hydroxide solution (8.0 ml, 0.016 mol) was added to a solution of (E)-3-(3-methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxycinnamic acid t-butyl ester (Example 12; 1.8 g, 0.004 mol) in methanol (8 ml) and the mixture heated under reflux for 5 hours. The methanol was removed by evaporation under vacuum and the aqueous solution acidified to pH 1 with 2N hydrochloric acid. Exhaustive extraction of the product with 10% methanol in ethyl acetate was followed by drying of the combined extracts ($Na_2SO_4$) and evaporation of solvents under vacuum to furnish an off-white solid. Crystallisation from ethyl acetate-methanol afforded the title compound as white crystals (0.18 g, 12%), m.p. 231-232°C. Found: C,63.52; H,5.96; N,14.00. $C_{21}H_{24}N_4O_4$ requires C,63.62; H,6.10; N,14.13%.

EXAMPLE 14

N-[(E)-3-(3-Methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxy-cinnamoyl]morpholine

To a stirred solution of (E)-3-(3-methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxycinnamic acid (Example 13; 1.0 g, 0.0025 mol) and morpholine (0.21 g, 0.0025 mol) in dichloromethane at 0°C was added, sequentially, N-methylmorpholine (0.5 g, 0.005 mol), 1-hydroxybenzotriazole hydrate (0.383 g, 0.0025 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.957 g, 0.005 mol). The reaction mixture was allowed to warm to room temperature, stirred for 20 hours and evaporated under vacuum, then the residue partitioned between water (30 ml) and dichloromethane (30 ml). The organic phase was removed and the aqueous phase extracted with more dichloromethane (2 x 30 ml); the combined organic solutions were then dried ($Na_2SO_4$) and the solvent removed under vacuum to give a white solid. Purification by column chromatography ($SiO_2$, $CH_2Cl_2$ then 3% MeOH in $CH_2Cl_2$) and crystallisation from ethyl acetate-hexane-methanol afforded the title compound as white crystals (0.74 g, 63%), m.p. 156-157°C. Found: C,64.60; H,6.85; N,15.16. $C_{25}H_{31}N_5O_4$ requires C,64.50; H,6.71; N,15.04%.

EXAMPLE 15

N-{3-[3-(3-Methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxyphenyl]-propanoyl}morpholine

A solution of N-[(E)-3-(3-methyl-4-oxo-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-n-propoxycinnamoyl]morpholine (0.5 g, 0.0011 mol) in ethanol (30 ml) was stirred with 10% palladium on charcoal catalyst (0.05 g) under a hydrogen pressure of 50 p.s.i. (3.45 bar) at room temperature for 14 hours.

The reaction mixture was filtered and solvent removed by evaporation under vacuum. Trituration of the residue with diethyl ether, followed by crystallisation from ethyl acetate-hexane, afforded the title compound as white crystals (0.37 g, 74%), m.p. 132-133°C. Found: C,64.39; H,7.26; N,14.80. $C_{25}H_{33}N_5O_4$ requires C,64.22; H,7.11; N,14.98%.

PREPARATION 1

5-Amino-1-n-propylpyrazole-4-carboxamide

A solution of 5-amino-4-cyano-1-n-propylpyrazole (J. Med. Chem., 1968, 11, 79; 4.0 g, 0.0027 mol) in a mixture of concentrated sulphuric acid (30 ml) and water (3 ml) was heated at 90°C for 1 hour. The cool reaction mixture was poured into ice/water (70 g) and the resulting mixture basified with solid sodium carbonate to pH 8. The aqueous solution thus obtained was extracted with ethyl acetate (5 x 100 ml), the combined extracts dried ($Na_2SO_4$) and the solvent removed by evaporation under vacuum to give the title compound as a pale yellow solid (4.25 g, 95%). A sample was obtained as colourless crystals, m.p. 183-185°C, by crystallisation from methanol-diethyl ether. Found: C,50.39; H,6.94; N,33.21. $C_7H_{12}N_4O$ requires C,49.99; H,7.19; N,33.31%.

PREPARATION 2

5-(2-Ethoxybenzamido)-1-n-propylpyrazole-4-carboxamide

2-Ethoxybenzoyl chloride (0.73 g, 0.0039 mol) was added dropwise to a solution of 5-amino-1-n-propylpyrazole-4-carboxamide (0.56 g, 0.0033 mol) in pyridine (10 ml) and the resulting mixture stirred at room temperature for 20 hours under a dry nitrogen atmosphere. The solvent was removed by evaporation under vacuum and the residue partitioned between dichloromethane (30 ml) and saturated aqueous sodium carbonate solution (30 ml). The organic layer was removed and the aqueous layer extracted with more dichloromethane (2 x 30 ml). The combined organic extracts were dried ($Na_2SO_4$) and then evaporated under vacuum. The yellow oil thus obtained was purified by column chromatography ($SiO_2$, 5% MeOH in $CH_2Cl_2$) to give the product as a white solid (0.78 g, 74%). A sample was obtained as colourless crystals, m.p. 155-157°C, by crystallisation from ethyl acetate-methanol.

Found: C,60.98; H,6.45; N,17.78. $C_{16}H_{20}N_4O_3$ requires C,60.75; H,6.37; N,17.71%.

PREPARATION 3

6-(5-Chlorosulphonyl-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

6-(2-Ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 1; 0.5 g, 0.0017 mol) was added portionwise to stirred chlorosulphonic acid (3 ml) at 0°C and the resulting solution stirred at room temperature for 14 hours. The reaction mixture was then added dropwise to ice/water (20 g) and the aqueous solution thus obtained was extracted with dichloromethane (4 x 30 ml). The combined extracts were dried ($Na_2SO_4$) and the solvent evaporated under vacuum to give a white solid; trituration with diethyl ether (50 ml) gave the title compound (0.67 g, 100%), m.p. 177-180°C, which was used without further purification.

PREPARATION 4

6-(5-Bromoacetyl-2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Aluminium trichloride (1.34 g, 0.010 mol) was added portionwise to a stirred solution of 6-(2-ethoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (Example 1; 1.0 g, 0.0034 mol) and bromoacetyl bromide (1.35, 0.0067 mol) in dichloromethane (30 ml) at 0°C. The reaction solution was allowed to warm to room temperature, stirred for 14 hours, then for a further 2 hours under reflux. The cool reaction mixture was added dropwise to ice/water (50 g) and the resulting mixture stirred for 1 hour. The organic phase was separated and the aqueous phase extracted with dichloromethane (2 x 50 ml); the combined organic solutions were then washed with brine (10 ml) and dried ($Na_2SO_4$). Removal of the solvent by

evaporation under vacuum gave an off-white solid which, when triturated with ether (20 ml) and dried, afforded the product as a white solid (1.29 g, 92%). A sample crystallised from ethyl acetate-hexane as colourless crystals, m.p. 164-166°C. Found: C,51.88; H,4.56; N,13.13. $C_{18}H_{19}BrN_4O_3$ requires C,51.56; H,4.57; N,13.36%.

PREPARATION 5

5-Amino-4-cyano-3-methyl-1-n-propylpyrazole

Sodium methoxide (0.73 g, 0.0135 mol) was added to a suspension of n-propylhydrazine oxalate (1.05 g, 0.0064 mol) in methanol (20 ml) and the mixture stirred for 2 hours at room temperature. (1-Ethoxy-ethylidene)malononitrile (0.88 g, 0.0064 mol) was then added portionwise over 10 minutes and the resulting mixture heated under reflux for 4 hours. The reaction mixture was allowed to cool and the solvent removed by evaporation under vacuum. Dichloromethane (20 ml) was added to the residue and, after vigorous stirring of the mixture, the suspension was filtered. The filtrate was evaporated under vacuum and the residue purified by column chromatography ($SiO_2$, 2% MeOH in $CH_2Cl_2$) to give the title compound as pale brown crystals (0.50 g, 48%). A sample crystallised from ethyl acetate as pale brown needles, m.p. 104-105°C. Found: C,58.82; H,7.30; N,34.13. $C_8H_{12}N_4$ requires C,58.52; H,7.37; N,34.12%.

PREPARATION 6

5-Amino-3-methyl-1-n-propylpyrazole-4-carboxamide

By the same method as Preparation 1, the title compound was obtained from 5-amino-4-cyano-3-methyl-1-n-propylpyrazole (2.0 g, 0.012 mol), concentrated sulphuric acid (30 ml) and water (3 ml) as a white solid (2.19 g, 98%). A sample crystallised from methanol-ethyl acetate as colourless crystals, m.p. 165-166°C. Found: C,53.02; H,7.87; N,30.75. $C_8H_{14}N_4O$ requires C,52.73; H,7.74; N,30.75%.

PREPARATION 7

3-Methyl-5-(2-n-propoxybenzamido)-1-n-propylpyrazole-4-carboxamide

The title compound was prepared from 2-n-propoxybenzoyl chloride (5.33 g, 0.027 mol)and 5-amino-3-methyl-1-n-propylpyrazole-4-carboxamide (Preparation 6; 4.07 g, 0.022 mol) in pyridine (100 ml), following the procedure of Preparation 2, and was obtained as a white solid (5.84 g, 76%). A sample was crystallised from ethyl acetate-hexane, m.p. 111-113°C. Found: C,62.83; H,7.09; N,16.26. $C_{18}H_{24}N_4O_3$ requires C,62.77; H,7.02; N,16.27%.

PREPARATION 8

6-(5-Chlorosulphonyl-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

The title compound was prepared from 3-methyl-6-(2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo-[3,4-d]pyrimidin-4-one (Example 9; 0.5 g, 0.0017 mol) and chlorosulphonic acid (3 ml), by the same procedure as Preparation 3, and was obtained as a white powder (0.587 g, 90%), m.p. 148-150°C. Found: C,50.88; H,4.67; N,13.30. $C_{18}H_{21}ClN_4O_4S$ requires C,50.88; H,4.98; N,13.19%.

Biological activity

The following Table illustrates the in vitro activities for a range of the compounds of the invention.

TABLE

IN VITRO PDE INHIBITORY DATA:

SELECTIVITY BETWEEN CALCIUM/CALMODULIN (Ca/CAM)-INDEPENDENT cGMP PDE AND cGMP-INHIBITED cAMP PDE

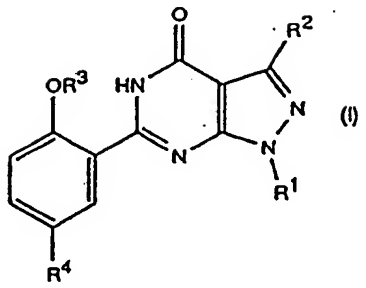
| EXAMPLE | $IC_{50}$(nM) cGMP | cAMP | SELECTIVITY RATIO |
|---|---|---|---|
| 2 | 8.6 | 51,000 | 5,930 |
| 3 | 14 | 63,000 | 4,500 |
| 4 | 32 | 45,000 | 1,406 |
| 5 | 44 | 45,000 | 1,022 |
| 8 | 13 | 10,000 | 769 |
| 10 | 1.0 | 20,000 | 20,000 |
| 13 | 1.0 | 64,000 | 64,000 |
| 14 | 0.58 | 46,000 | 79,310 |
| 15 | 1.3 | 65,000 | 50,000 |

Safety profile

Example 3 has been tested at therapeutic doses of up to 1 mg/Kg i.v. in rabbit with no signs of adverse acute toxicity being observed.

CLAIMS

1. A compound of formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein $R^1$ is $C_1$-$C_6$ alkyl;

$R^2$ is H, methyl or ethyl;

$R^3$ is $C_2$-$C_4$ alkyl;

$R^4$ is $C_1$-$C_4$ alkyl optionally substituted with $NR^5R^6$, CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkenyl optionally substituted with CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkanoyl optionally substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or halo;

$R^5$ and $R^6$ are each independently H or $C_1$-$C_4$ alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, 4-($NR^8$)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted by one or two $C_1$-$C_4$ alkyl groups;

$R^7$ is H or $C_1$-$C_4$ alkyl;

and $R^8$ is H, $C_1$-$C_3$ alkyl or hydroxy $C_2$-$C_3$ alkyl.

2. A compound as claimed in claim 1 wherein $R^1$ is n-propyl; $R^2$ is H or methyl; $R^3$ is ethyl or n-propyl; $R^4$ is ethyl substituted with $CONR^5R^6$ or $CO_2R^7$; vinyl substituted with $CONR^5R^6$ or $CO_2R^7$; acetyl substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or bromo; $R^5$ and $R^6$ together with the nitrogen atom to which they are

attached form a morpholino, 4-($NR^8$)-1-piperazinyl or 2,4-dimethyl-1-imidazolyl group; $R^7$ is H or t-butyl; and $R^8$ is methyl or 2-hydroxyethyl.

3. A compound as claimed in claim 2 wherein the said compound is selected from:

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and 3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and pharmaceutically acceptable salts thereof.

4. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, together with a pharmaceutically acceptable diluent or carrier.

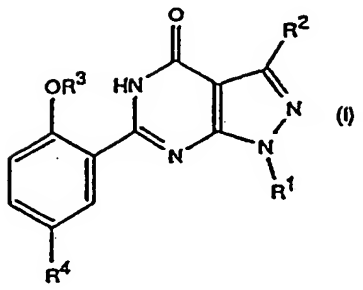
5. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 4, for use in medicine.

6. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 4, for the manufacture of a medicament for the treatment of

stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

7. A method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, condtions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility, in a mammal (including a human being), which comprises administering to said mammal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 4.

8. A process for the preparation of a compound of formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein $R^1$ is $C_1$-$C_6$ alkyl;

$R^2$ is H, methyl or ethyl;

$R^3$ is $C_2$-$C_4$ alkyl;

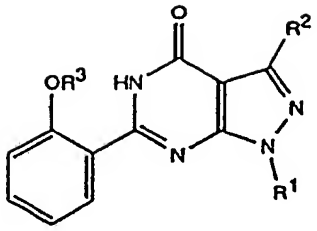
$R^4$ is $C_1$-$C_4$ alkyl optionally substituted with $NR^5R^6$, CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkenyl optionally substituted with CN, $CONR^5R^6$ or $CO_2R^7$; $C_2$-$C_4$ alkanoyl optionally substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or halo;

$R^5$ and $R^6$ are each independently H or $C_1$-$C_4$ alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, 4-($NR^8$)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted by one or two $C_1$-$C_4$ alkyl groups;

$R^7$ is H or $C_1$-$C_4$ alkyl;

and $R^8$ is H, $C_1$-$C_3$ alkyl or hydroxy $C_2$-$C_3$ alkyl;

which comprises reacting a compound of formula:



(II)

wherein $R^1$, $R^2$ and $R^3$ are as previously defined in this claim, for a compound of formula (I) when $R^4$ is

(A) $C_2$-$C_4$ alkanoyl,

with an acyl halide of formula ($C_1$-$C_3$ alkyl)COY wherein Y is halo, in the presence of a Lewis acid;

(B) $C_2$-$C_4$ alkanoyl substituted with $NR^5R^6$ wherein $R^5$ and $R^6$ are as previously defined in this claim,

with a haloacyl halide of formula X($C_1$-$C_3$ alkylene)COY wherein X is halo and Y is as previously defined in this claim, in the presence of a Lewis acid, followed by reaction of the resulting haloketone either with an amine of formula $R^5R^6NH$, or with a protected amine of formula $R^5NHP$, $R^6NHP$ or $P'_2NH$ wherein P and P' are suitable amine protecting groups followed by removal of P or P';

(C) halo wherein halo is fluoro, chloro, bromo or iodo,

under aromatic nitration conditions, followed by reduction of the resulting nitro compound to the corresponding primary amine, and subjection of the said amine to a conventional diazotisation-halogenation sequence;

(D) $C_1$-$C_4$ alkyl optionally substituted with $NR^5R^6$, CN, $CONR^5R^6$ or $CO_2R^7$ wherein $R^5$, $R^6$ and $R^7$ are as previously defined in this claim, or bromo,

(i) under chloromethylation conditions, followed by subjection of the resulting chloromethyl intermediate to, respectively
(a) reduction, or
(b) reaction with an amine of formula $R^5R^6NH$, or
(c) reaction with an alkali metal cyanide and optionally converting the resulting nitrile to the corresponding amide, acid or ester; or

(ii) under aromatic bromination conditions, followed by subjection of the resulting bromo derivative to, respectively,
(a) lithium-bromine exchange, followed by reaction of the aryllithium derivative with ethylene oxide to give the 2-hydroxyethyl derivative, or
(b) reaction with allyl alcohol, followed by catalytic hydrogenation of the alkene to give the 3-hydroxypropyl derivative, or
(c) reaction of 3-buten-1-ol, followed by catalytic hydrogenation of the alkene to give the 4-hydroxybutyl derivative,
and conversion of any of the foregoing alcohols to the corresponding alkane, amine or nitrile by activation of their respective hydroxy groups to give the intermediate chloride, bromide, iodide or mesylate followed by reduction, or reaction with an amine of formula $R^5R^6NH$, or reaction with an alkali metal cyanide, respectively, and further optional conversion of the said nitrile to the corresponding amide, acid or ester;

(E) $C_2$-$C_4$ alkenyl 2-substituted with CN, $CONR^5R^6$ or

$CO_2R^7$, or $C_2$-$C_4$ alkyl 2-substituted with CN, $CONR^5R^6$, $CO_2R^7$ or $CH_2NH_2$, wherein $R^5$, $R^6$ and $R^7$ are as previously defined in this claim,

via the bromo derivative of (D) (ii) above, with the appropriate α,β-unsaturated nitrile, amide or ester respectively, optionally followed by hydrolysis of any resulting ester, reduction of the resulting alkenyl group and, in the case of the nitrile, further or concomitant reduction of the nitrile group to the corresponding primary amine;

(F) $C_2$-$C_4$ alkenyl, or $C_2$-$C_4$ alkyl, each optionally substituted with CN, $CONR^5R^6$ or $CO_2R^7$ wherein $R^5$, $R^6$ and $R^7$ are as previously defined in this claim,

via the bromo derivative of (D) (ii) above, with a lithium-bromine exchange reagent, followed by subjection of the aryllithium derivative to formylation, and reaction of the resulting aldehyde with the appropriate optionally CN-, $CONR^5R^6$- or $CO_2R^7$-substituted $C_1$-$C_3$ alkyl phosphonium salt or phosphonate, optionally followed by hydrolysis of any resulting ester and reduction of the resulting alkenyl group;

(G) $CONR^5R^6$ or $CO_2R^7$ wherein $R^5$, $R^6$ and $R^7$ are as previously defined in this claim,

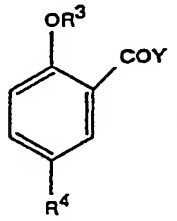
via the bromo derivative of (D) (ii) above, with a lithium-bromine exchange reagent, followed by reaction of the aryllithium derivative with carbon dioxide, and conversion of a suitably activated form of the resulting carboxylic acid to an amide or ester derivative by reaction with an amine of formula $R^5R^6NH$ or alcohol of formula $R^7OH$ respectively;

(H) $SO_2NR^5R^6$ wherein $R^5$ and $R^6$ are as previously defined in this claim,

with a halosulphonation reagent, followed by reaction of the resulting sulphonyl halide with an amine of formula $R^5R^6NH$;

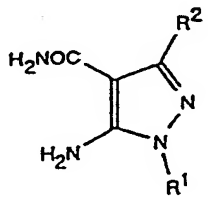
followed in each case, by optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

9. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^1$, $R^2$, $R^3$ and $R^4$ are as previously defined in claim 8, which comprises reacting a compound of formula:




(XI)

wherein Y is chloro or bromo, and $R^3$ and $R^4$ are as previously defined in claim 8, with an aminopyrazole of formula:




(VIII)

wherein $R^1$ and $R^2$ are as previously defined in claim 8,

followed by cyclisation of the resulting amide by treatment with a base, optionally in the presence of hydrogen peroxide, and optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

10. A process as claimed in claim 8 wherein

in (A), Y is chloro or bromo, and the Lewis acid is aluminium chloride or aluminium bromide;

in (B), X and Y are chloro or bromo, P is benzyl and is removed by catalytic hydrogenation, and P′ is t-butoxycarbonyl and is removed using hydrogen chloride;

in (C), the nitration is achieved using concentrated nitric acid in combination with concentrated sulphuric acid, and the nitro compound is reduced by catalytic hydrogenation;

in (D),

(i) the chloromethylation is carried out using paraformaldehyde and concentrated hydrochloric acid, and

(a) the reduction is effected by palladium-catalysed hydrogenation,

(b) the reaction with $R^5R^6NH$ is carried out using an excess of said amine,

(c) the alkali metal cyanide is sodium cyanide or potassium cyanide;

(ii) the aromatic bromination is carried out using N-bromosuccinimide, and

(a) the lithium-bromine excchange is effected using n-butyllithium,

(b) the reaction with allyl alcohol is effected under Heck reaction conditions,

(c) the reaction with 3-buten-1-ol is effected under Heck reaction conditions;

in (E), the reaction with the appropriate α,β-unsaturated nitrile, amide or ester respectively is effected under Heck reaction conditions using tri-o-tolylphosphine, palladium(II) acetate and triethylamine, the optional hydrolysis of the ester is achieved using aqueous sodium hydroxide solution in methanol, the optional reduction of the alkenyl group is effected by palladium-catalysed hydrogenation, and the optional further or concomitant reduction of the nitrile group is carried out using Raney nickel in glacial acetic acid;

in (F), the lithium-bromine exchange is effected using n-butyllithium, the formylation reagent is dimethylformamide, and the alkene reduction is achieved by catalytic hydrogenation;

in (G), the lithium-bromine exchange is effected using n-butyllithium, and the carboxylic acid is activated using a carbodiimide in combination with 1-hydroxybenzotriazole;

in (H), the halosulphonation reagent is chlorosulphonic acid, and the reaction with $R^5R^6NH$ is carried out using an excess of said amine.

11. A process as claimed in any one of claims 8 to 10 wherein $R^1$ is n-propyl; $R^2$ is H or methyl; $R^3$ is ethyl or n-propyl; $R^4$ is ethyl substituted with $CONR^5R^6$ or $CO_2R^7$; vinyl substituted with $CONR^5R^6$ or $CO_2R^7$; acetyl substituted with $NR^5R^6$; $SO_2NR^5R^6$; $CONR^5R^6$; $CO_2R^7$; or bromo; $R^5$ and $R^6$ together with the nitrogen atom to which they are attached form a morpholino, 4-($NR^8$)-1-piperazinyl or 2,4-dimethyl-1-imidazolyl group; $R^7$ is H or t-butyl;

and $R^8$ is methyl or 2-hydroxyethyl.

12. A process as claimed in claim 11 wherein the said compound of formula (I) produced is selected from:

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and 3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and pharmaceutically acceptable salts thereof.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/02237

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; A61K31/505; //(C07D487/04,239:00,231:00)

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D ; A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| A | EP,A,0 349 239 (SMITH KLINE & FRENCH) 3 January 1990 cited in the application see page 3, line 1 - page 3, column 7; claims 1,9 | 1,6 |
| A | EP,A,0 201 188 (WARNER-LAMBERT) 17 December 1986 cited in the application see claims 1,8,9 | 1,6 |
| P,A | EP,A,0 463 756 (PFIZER) 2 January 1992 see claims 1,7 | 1,6 |

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 08 JANUARY 1993 | 21. 01. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | VOYIAZOGLOU D. |

# INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/EP 92/02237

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark:Although claim 7 is directed to a method of treatment(diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9202237 SA 65591

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/01/93

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP-A-0349239 | 03-01-90 | AU-B- 614389 | 29-08-91 |
| | | AU-A- 3709989 | 04-01-90 |
| | | JP-A- 2056484 | 26-02-90 |
| | | US-A- 5075310 | 24-12-91 |
| EP-A-0201188 | 17-12-86 | US-A- 4666908 | 19-05-87 |
| | | JP-A- 61236778 | 22-10-86 |
| EP-A-0463756 | 02-01-92 | AU-B- 626757 | 06-08-92 |
| | | AU-A- 7915591 | 19-03-92 |
| | | CN-A- 1057464 | 01-01-92 |